DYNAMICS OF THE CIRCULATION AND OF AIRFLOW AND MECHANISMS OF CARDIORESPIRATORY ADJUSTMENT

MEDICAL COLLEGE OF VIRGINIA
RICHMOND, VIRGINIA

1976

Final Summary Report

Office of Naval Research Contract #N-00014-68-A-0510-0003

For the Period

11/1/69 --- 10/31/72

Title of Contract

Dynamics of the Circulation and of Airflow and Mechanisms of Cardiorespiratory Adjustment

Contractor: Medical College of Virginia
Health Sciences Division
Virginia Commonwealth University

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Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Dynamics of the Circulation and of Airflow and Mechanisms of Cardiorespiratory Adjustment		5. TYPE OF REPORT & PERIOD COVERED Final Summary 11/1/69 10/31/72 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) John L. Patterson, Jr., M.D. H. Page Mauck, Jr., M.D.		8. CONTRACT OR GRANT NUMBER(s) N00014-68-A-0510-0003
9. PERFORMING ORGANIZATION NAME AND ADDRESS Medical College of Virginia Health Sciences Division Virginia Commonwealth Univ., Richmond, Va.		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS NR 101-607
11. CONTROLLING OFFICE NAME AND ADDRESS Office of Naval Research (Code 441) 800 N. Quincy St. Arlington, Va. 22217		12. REPORT DATE 1976 13. NUMBER OF PAGES //
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Unlimited Distribution

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Circulation
Respiratory Airflow
Baroreceptor
Pulmonary Gradient
Cardiac Rhythm
Cardiac Control
Atrial Distention
Head Injury

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The investigations carried out under this contract were designed to clarify basic physiologic mechanisms in certain areas of circulation and respiration. In pursuing these studies, new techniques were developed for studying the dynamic mechanisms involved. The results and techniques are discribed briefly and appropriate publications are cited in the bibliography.

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S/N 0102-LF-014-6601

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

The investigations carried out under this contract were designed to clarify basic physiologic mechanisms in certain areas of the circulation and respiration. In pursuing our studies of these dynamic mechanisms, we have undertaken the development of new techniques whenever this was found to be essential to achieving the specific aims of the projects.

I. Neural control of cardiac rhythm and conductivity.

These studies on dogs, cats and squirrel monkeys were designed to clarify the relative importance of sympathetic and parasympathetic components of autonomic nervous control of the heart in the production of cardiac arrhythmias. Additionally, we sought to assess the influence of these factors on blood pressure and distribution of blood flow.

Stereotaxic orientation of electrodes has enabled their placement into regions of the sub-cortex capable of eliciting strong sympathetic or parasympathetic efferent discharges. The findings of many experiments strongly support the view that a delicate balance exists between the two primary branches of the autonomic nervous system, a balance which exerts to a major degree control of cardiac rate, rhythm, and, to some extent, intracardiac conduction. The results of selected studies follow.

Graded increments in electrical stimuli to selected areas of the mesencephalon and to the distal right vagus, performed both simultaneously and in sequence, have supported the concept that sympathetic stimulus from mesencephalic regions is capable of overriding a strong vagal stimulus. It was possible to produce ventricular tachycardia by sympathetic stimulation. The latter stimulus at its cessation, is followed by vagal stimulation alone which slows ventricular rate below control levels without altering the ECG. These findings support the concept that there exists a significant degree of vagal influence on the myocardium under the conditions of these experiments, and that both divisions act in concert when one branch is activated.

Stimulation of certain regions of the diencephalon have produced predominantly parasympathetic discharges while stimulation of others has evoked sympathetic responses. Stimulation of certain regions in the anterior hypothalamus was followed by shift in the sinoatrial pacemaker and frequently sinoatrial arrest. Also activation of regions of the cingulate gyrus is capable of eliciting atrial flutter and fibrillation which is abolished with bilateral section of the vagi. Evocation of these arrhythmias from high neural centers rostral to the medulla was first made under this contract. Pure acute arterial hypoxia, i.e. with eucapnea, enhanced the exhibition of these arrhythmias but an additive effect was observed when mild hypercapnea was introduced.

Experiments were performed to assess the effects of environmental stimuli on cardiovascular function. The Sidmann avoidance reaction served as the experimental stimulus. In this, the presentation of a red light had to be followed by a rapid response on the part of the animal (pressing on a lever) to avoid an ensuing mildly painful tail shock. An occasional animal showed bradycardia followed by A-V dissociation, fall in blood pressure, and ventricular arrest, but elevation of pressure and tachycardia were more common. Certain features of the results suggested that the stress of decision-making and pressing the lever to avoid the stimulus produced the changes in heart rate and rhythm, and in blood pressure, rather than the pain itself. Pathologic changes were seen in the myo-

cardium of animals who were able to avoid the pain stimulus, changes that were much rarer in the myocardia of the animals than received the stimulus of pain.

These investigations as a whole have clearly documented the importance of the autonomic nervous system, including specific regions of the mid-brain, in the production of changes and abnormalities in heart rate, rhythm, and blood pressure.

II. Response of the denervated heart to hemorrhage.

The study of the response of the denervated heart to mild hemorrhage was undertaken to determine the degree of impairment of the cardiovascular compensation in the absence of extrinsic neural cardiac control. It was found that under pentobarbital and α-chloralose-urethane anesthesia, the dogs with cardiac autotransplantation did not respond with an increase in heart rate following small reductions in blood volume. On the other hand, control animals under the same conditions did respond with an increase in heart rate, the only distinguishing abnormality between these two groups of animals. This result implies that the tachycardia observed in normal dogs is mediated by changes in cardiac sympathetic activity and not through circulating catecholamines.

Determinations of plasma renin activity on both control and autotransplanted dogs revealed a subnormal increase in plasma renin activity relative to the activity level shown in normal dogs. The possibility is thus raised that reflexes from the heart might be important in the regulation of blood volume, a view long held by Gauer, Henry and others, and that their effects may well be mediated through changes in plasma renin activity. Increased blood volume is a known consequence of cardiac autotransplantation in the dog, a finding which we have confirmed (observations).

III. The Elevation Gradient of Lung Density and Its Components.

Some years ago, this laboratory produced an analysis of the gradient of intrapleural pressure in the direction of the gravity vector (Krueger, J., Bain, T. and Patterson, J. L., Jr., The elevation gradient of intrathoracic pressure. J. Appl. Physiol. 16:465, 1961). In these experiments, the mean density of the animal's lungs was almost identical to the intrapleural pressure gradient. These values were respectively 0.22 gm/cm descent and 0.21 gm/cm^3. We theorized that the lung was acting, insofar as the pressure gradient was concerned, as a homogeneous fluid. More recent studies demonstrated the existence of a large gradient of lung density in the vertical direction. We believe this measurement to be highly accurate, since in the animal held in the upright position, the heart was fibrillated, the trachea clamped, and the chest opened, the hilar vessels tied, and the entire lung-heart system removed in the vertical position, wrapped in Mylar^R in the same position, and immersed in liquid air within 1½ minutes. The average lung density at the apex, determined by sawing out cubes of the frozen tissue, measuring them and weighing them, was 0.1 gm/cm cubed and the density of the base 3 to 3.5 times as great. The density gradient was reversed in animals held in the inverted position, but the gradient itself was less marked in this position, and in animals maintained in the horizontal position the apex to base was small but still present, a fact suggesting that shift of blood alone might not have been the sole factor in the observed density differences. This conclusion was supported by the findings on the components of lung density: blood, tissue, gas. The blood component was determined by finely grinding the sawn cube of lung tissue, analyzing for alkaline oxyhemoglobin, and converting the result to the

relative contribution of blood to the measured density. Since the relative contribution of gas to the density was nearly zero, the three components could be calculated.

An equation relating the intrathoracic pressure to the density gradient was quite similar to the equation relating density to pressure in the compressible atmosphere. Since the mean density of the dog's lung is comparable to that of man, we can reasonably expect to extrapolate the findings in the animals to the somewhat greater apex to base distance in man. This would indicate that in the upright position, the base of the human lung is approximately four times the density of the apex.

The findings are applicable not only to normal physiology and the pathophysiology of the lungs on earth, but also have suggestive applications to respiratory function in the weightless state.

IV. Elevation gradient of lung density with increased blood volume.

Hypervolemia, induced by mass infusion of either high molecular weight dextran or pooled fresh whole blood, produced the following results on the quick-frozen lungs of animals held in the vertical position: First, there was a statistically significant increase in the mean density of the hypervolemic lung as compared with that in normovolemic controls. The mean density, in reference to a specified locus, was 0.24 grams per cc in the hypervolemic animals as compared to 0.19 in the controls, representing an increase in mean density of 30% ($p<0.05$). Secondly, there was a decrease in the density gradient from that seen in normovolemic controls - the density in the apex increased while the density in the base remained about the same. The increased lung density we interpret as having been due to increased pulmonary blood volume.

V. Influence of local metabolites on peripheral blood flow.

In an attempt to determine whether or not the hypercapnic acidosis might be of major importance in bringing about the vasodilator response to ischemia, studies were performed on the gastrocnemious muscle of the dog perfused at constant flow. Perfusion pressure was monitored and used as a measure of the changes in vascular resistance in the course of the experiments. Hypercapnic acidosis, produced locally by the intra-arterial infusion of a buffered isotonic mixture of hydrochloric acid and glycine, was found to be vasodilator in the dog although the response was less pronounced than in man. Subsequently, the findings during production of ischemia in conjunction with the intra-arterial infusion of the acid were compared to the vasodilator response of ischemia alone. The results indicated that hypercapnic acidosis could account for 2/3 of the vasodilator response to ischemia.

VI. Investigation of the bradypnea response in dogs following left atrial distention.

While the effects of mechanical stimulation of both right and left atrial receptors on heart rate and blood pressure have been studied by many different groups, relatively little work has been done to evaluate the role of the atrial receptors in the regulation of breathing. The effect on respiratory rate after sudden balloon inflation in the left atrium were studied in three groups of dogs: dogs anesthetized with alpha-chlorolose, dogs anesthetized with

sodium pentobarbital, and dogs studied in the awake state. The detailed results of these experiments suggest that two opposing reflexes are operating during left atrial distention. Tachypnea may result from sensitization of pulmonary stretch receptors secondary to pulmonary vascular engorgement and the hitherto undescribed bradypnea response might be mediated by left atrial receptors, known to exist. The postmortem identification of the site of the balloon near the mitral orifice would suggest that receptors mediating the bradypnea response might well be situated in tissues surrounding the mitral ring. All of these results indicate that the bradypnea response was indeed a reproducible phenomenon and that it could be produced most frequently in the series of dogs anesthetized with α-chlorolose.

VII. Mechanism of baroreceptor-induced changes in heart rate.

In recent years, studies have suggested that increases in heart rate in response to systemic hypotension are mediated exclusively by increased sympathetic activity while decreases in heart rate in response to systemic hypertension are due solely to increases in parasympathetic activity. This concept does not support the classical view that reciprocal changes in parasympathetic and sympathetic efferent activity are involved.

In this study, the beta-adrenergic receptor blocker propanolol reduced significantly but did not abolish tachycardia in response to the hypotension induced by intravenous nitroglycerin. It also reduced significantly the bradycardia in response to hypertension produced by intravenous phenylephrine. Parasympathetic efferent blockade with atropine essentially abolished the tachycardia in response to nitroglycerin and the bradycardia in response to phenylephrine. Propanolol reduced but did not abolish the tachycardia in response to bilateral carotid arterial occlusion. Parasympathetic blockade with atropine reduced but did not abolish the bradycardia in response to bilateral electrical stimulation of the carotid sinus nerves. These findings indicate that baroreceptor-induced changes in heart rate are mediated by reciprocal alterations in cardiac parasympathetic and sympathetic efferent activity.

VIII. Circulation and respiration in induced acute head injury.

This collaborative investigation with the Department of Physiology began from an incidental observation in the course of obtaining specimens of domestic cow lungs from a local abbatoir. Following stunning with the sledge hammer (in use at time of the beginning of these studies) apnea ensued in the unconscious animal, sometimes followed by gradual irregular resumption of respiration, and in other animals continuing into permanent apnea. Auscultation of the animal's heart with the stethoscope showed a continuation of normal or near-normal heart sounds for several minutes. It was clear that failure of neural respiratory control was occurring in all of the animals immediately after they were stunned into the unconscious state, whereas the circulation appeared to be maintained. This was confirmed by the first experiment in which arterial pressure was recorded at heart level both before and after the head injury by means of strain gauge and a direct writing recorder, and led to the series being continued both at the local abbatoir and for studies on a tracheostomized cow at the U.S. Agricultural Experiment Station, Beltsville, Maryland. The studies were initiated during earlier Office of Naval Research contracts, and the final 3 animals were completed during the contract that is the subject of this report.

A total of 21 cows has been studied. Head injury was produced with a heavy sledge hammer in the initial series, and later with the more modern captive bolt pistol. In either case, depressed fractures were produced, with gross hemorrhage on or near the surface of the brain. Petechial hemorrhages and perivascular cuffs of red cells were seen throughout the brain. Every animal stopped breathing in the period immediately following head injury. Approximately 40% of the animals later resumed spontaneous breathing, at first with small breaths of varying size and irregularly spaced, later with more regular and deeper breaths in some animals. In other animals respiration subsided again into apnea. Little difference was seen between the gross and microscopic brain findings in the animals that were able to resume breathing and those that did not. The arterial blood gas changes during the apnea were rapid, with hypoxia developing and becoming extreme and relatively stable after 6 to 8 minutes and with hypercapnia also developing and becoming marked and stable at about the same time. In animals who resumed breathing, the picture was different and variable. One animal, who was permanently apneic after the head injury was respired with a hand pump respirator for 75 minutes, the respirator being connected to a tracheostomy. It appeared that this animal could have been maintained indefinitely in this manner with normal arterial blood gases, normal electrocardiogram, and normal intravascular pressures if an electrically powered respirator of adequate size had been available.

In the permanently apneic animals, the cardiac output by indicator dilution technique was well-maintained in the initial minutes after the head injury. This was also true of arterial pressure, which in almost every animal, was maintained after the head injury at either control level or higher for at least 3 minutes. Somewhere between 3 and 7 minutes post-head injury the pressure began to decline until it became unrecordable after 12 to 18 minutes. Only a few animals showed major arrhythmia in the early post-injury period. Supraventricular and ventricular arrhythmias appeared during the period of low and falling blood pressure.

Major therapeutic lessons can be drawn from these findings, applicable both to head injury in the military and civilian life. The Principal Investigators had two personal experiences with similar findings in man: one following crash of a service aircraft, in which the temporarily surviving pilot showed heart action, but was apneic, and another following crash of a college student's car into a tree. In the latter the patient was seen approximately 1 minute later, apneic with bounding pulse which became feeble only after about 8 to 10 minutes of apnea.

The pacemaker for respiration, being intracranial, is perculiarly vulnerable to head injury, whereas the cardiac pacemaker being extracranial, is far less vulnerable to the effects of head injury. Judging from the arterial O_2 and CO_2 tension and pH curves, it appears to us that the brain, if it does not reinstitute effective firing of the respiratory center within 4 or 5 minutes, becomes trapped by the blood gas changes resulting from the centers' inability to resume firing within that critical period.

We conclude that the requirement for those who arrive at the scene of an accident involving humans during that critical period is for prompt and effective mouth-to-mouth resusitation, a procedure far easier for non-medical personnel or personnel not trained for medical emergencies, whether civilian or military, than combined mouth-to-mouth resusitation and closed chest cardiac massage. If apnea continues, tracheal intubation and

maintenance on a respirator are obviously required. Awareness of the urgency to restore adequate pulmonary ventilation in completely apneic or hypoventilating individuals following head injury, with effective action based on this awareness, should save many lives, both in military and in civilian life.

IX. Physiology of acceleration and weightlessness.

Collaboration with Captain Ashton Graybiel, MC USN (Ret.) on a lengthy chapter entitled "Acceleration, Gravity and Weightlessness" (Patterson, J. L., Jr. and Graybiel, A. in ENVIRONMENTAL PHYSIOLOGY, Balfour Sionim, Editor, the C. V. Mosby Company, St. Louis, 1974.) This work was based on many years of collaboration with Captain Graybiel and colleagues over the period of several Office of Naval Research contracts. The collaboration on this chapter was begun intensively during the period of the recent contract that is the subject of this report and the work was completed after the contract's expiration. The collaboration took the form of many trips to the U.S. Navy's Aerospace Medical Institute, NAS, Pensacola, Florida, and was financed in part by contract funds, in part by local funds in the Medical College of Virginia and also by large investment of personal funds by the Principal Investigator. The library staff of the Aerospace Institute provided us with full cooperation and made a major contribution to the overall effort. The advice of a considerable number of members of the faculty of the Naval Aerospace Medical Institute was sought during the preparation of the manuscript and assistance was freely given.

This chapter and previous work at the former Naval School of Aviation Medicine and the present Naval Aerospace Medical Institute resulted in the Principal Investigator's election to membership in the International Academy of Astronautics in 1976.

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16. Experiments completed during contact and following its expiration; manuscript in preparation:

Hardie, E. L., Doyle, J.T., Said, S.I. and Patterson, J.L., Jr.

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